CLINICAL–ALIMENTARY TRACT

Cancer Incidence in a Population-Based Cohort of Individuals Hospitalized With Celiac Disease or Dermatitis Herpetiformis

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See editorial on page 1726.

Background & Aims: **Studies of cancer risk in celiac disease (CD) or dermatitis herpetiformis (DH) indicate increased risks for malignant lymphoma and occasionally other neoplasms, but are characterized by small numbers, lack of systematic cancer assessment, and subjects identified from referral institutions.** ***Methods:*** **By using Swedish population–based inpatient and cancer registry data, we followed-up 12,000 subjects with CD or DH, and evaluated cancer incidence by using standardized incidence ratios (SIR).** ***Results:*** **Adults (but not children and adolescents) with CD had an elevated overall risk for cancer (SIR = 1.3) that declined with time and eventually reached unity. Elevated risks were found for malignant lymphomas, small-intestinal, oropharyngeal, esophageal, large intestinal, hepatobiliary, and pancreatic carcinomas. The excess occurrence of malignant lymphomas was confined to adults, decreased with time of follow-up evaluation, and decreased over successive calendar periods. Decreased risks were found for breast cancer. Subjects with DH had a slightly increased overall cancer risk (SIR = 1.2) owing to excesses of malignant lymphoma and leukemia, but no increases of gastrointestinal carcinomas.** ***Conclusions:*** **Albeit increased, the relative risks for lymphomas and gastrointestinal cancers in this study are lower (and declining) than in most previous reports. The overall cancer risk is only moderately increased, and nonelevated during childhood and adolescence.**

Celiac disease (CD) and dermatitis herpetiformis (DH) are 2 interrelated conditions of abnormal gluten sensitivity, mostly occurring in genetically predisposed individuals.[1,2] The prevalence of diagnosed CD displays a geographic variation, with higher prevalence in Caucasian than in non-Caucasian individuals. Among Caucasians, the reported prevalence of biopsy specimen–proven disease has been higher in, for example, Ireland than in the United States. However, serologic studies in blood donors indicate a more homogenous prevalence of antibody positivity, which may point to underdiagnosis of the disease in, for example, the United States.[3–5] Several studies have reported that patients with CD or DH suffer from notably increased risks for non-Hodgkin's lymphoma and certain carcinomas of the gastrointestinal tract.[6–21] Accordingly, in a recent study, Italian patients with CD were at a 16-fold increased risk for dying from non-Hodgkin's lymphoma (16 cases among 1072 patients), which accounted for two thirds of all observed cancer cases.[20] In contrast, however, a second recent Italian study estimated only a 3-fold increased risk for lymphoma, though based on only 6 cases.[22] In brief, few of the hitherto published studies have followed-up large enough numbers of individuals to obtain stable risk estimates with regard to the risk for, and characteristics of, non-Hodgkin's lymphoma and gastrointestinal carcinomas.[7–10,12,13,15,16,20] With respect to other types of cancer, only small numbers of cases have been reported. Moreover, most of the previous studies have identified adult patients at referral centers or specialty clinics.[6–10,12,15,16,20,21] Consequently, little is known about the cancer pattern in less selected and population-based series of patients, in particular about the cancer risk after childhood-onset CD,[23] and how the cancer risk in CD compares with that of DH.[16]

To assess the cancer profile among patients with CD or DH, we performed a retrospective cohort study of some

Abbreviations used in this paper: CD, celiac disease; CI, confidence interval; DH, dermatitis herpetiformis; ICD, International Classification of Diseases; SIR, standardized incidence ratio.

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12,000 individuals with either disease by using data from the nationwide and population-based Swedish inpatient and cancer registers.

Patients and Methods

Patients

In Sweden, all inpatient care for CD during the study period was public and population based, and referral patterns were almost solely based on geographic (rather than financial or other) determinants. The inpatient register contains individual-based information on Swedish inpatient care on a countywide level since 1964, and nationwide since 1987.[24] For each hospitalization, the inpatient registry includes the patient's national registration number, unique to each citizen,[25] dates of admission and discharge, discharge diagnoses, surgical procedures, department, and hospital. Subjects eligible for this investigation included all individuals discharged at least once with a discharge diagnosis of CD (Swedish International Classification of Diseases [ICD], ICD-7: 286.00, ICD-8: 269.00, 269.98, ICD-9: 579A, n = 12,083) or DH (ICD-7: 704.00, ICD-8: 693.99, ICD-9: 694A, n = 1577) during the years 1964–1994. A total of 480 observations were excluded from the CD cohort and 112 from the DH cohort owing to nonmatching national registration numbers or other data irregularities. There were 226 subjects with both discharge diagnoses. A total of 8313 (72%) of the entire CD cohort had CD listed as the main discharge diagnosis on the first discharge featuring CD, and 9797 individuals (85%) had at least one discharge on which CD was the main discharge diagnosis. A total of 6696 individuals (58%) in the CD cohort had no other discharge diagnoses except CD listed on the initial discharge.

Table 2. SIR and 95% CI of Cancer in CD (Free From DH) and DH (Without CD) Identified in the Swedish Inpatient Register 1964–1994 and Followed-Up Through 1995

	CD		DH	
Site (ICD7)	*n*	SIR (95% CI)	*n*	SIR (95% CI)
All cancer (140–209)	249	1.3 (1.2–1.5)	135	1.2 (1.0–1.4)
Oral (140–148)	8	2.3 (1.0–4.5)	2	0.8 (0.1–3.0)
Esophagus (150)	6	4.2 (1.6–9.2)	2	1.8 (0.2–6.5)
Stomach (151)	6	0.9 (0.3–2.0)	8	1.4 (0.6–2.8)
Small intestine (152)	8	10 (4.4–20)	0	0.0 (0.0–7.0)
Large intestine (153)	26	1.9 (1.2–2.8)	9	1.0 (0.4–1.8)
Rectum (154)	6	0.8 (0.3–1.6)	4	0.7 (0.2–1.8)
Primary liver (155)	11	2.7 (1.3–4.7)	1	0.4 (0.0–2.0)
Pancreas (157)	9	1.9 (0.9–3.6)	4	1.2 (0.3–3.0)
Larynx (161)	2	2.2 (0.3–8.0)	2	2.7 (0.3–9.8)
Lung (161–163)	12	1.0 (0.5–1.7)	8	0.9 (0.4–1.8)
Melanoma (190)	4	0.6 (0.2–1.7)	3	1.0 (0.2–3.0)
Squamous skin (191)	8	1.1 (0.5–2.1)	9	1.6 (0.7–3.0)
Breast (170)	7	0.3 (0.1–0.5)	10	0.9 (0.4–1.6)
Uterus (171–174)	5	0.6 (0.2–1.3)	8	2.2 (0.9–4.3)
Ovary (175)	7	1.3 (0.5–2.7)	2	0.9 (0.1–3.3)
Testis (178)	1	1.2 (0.0–7.0)	0	0.0 (0.0–14)
Prostate (177)	14	0.7 (0.4–1.2)	17	0.9 (0.5–1.4)
Bladder (181)	14	1.7 (0.9–2.8)	10	1.5 (0.7–2.8)
Kidney (180)	5	0.9 (0.3–2.2)	4	1.2 (0.3–3.1)
Brain (193)	5	0.6 (0.2–1.4)	1	0.4 (0.0–2.3)
Thyroid (194)	1	0.6 (0.0–3.3)	1	1.3 (0.0–7.2)
Endocrine (195)	11	3.0 (1.5–5.3)	2	1.3 (0.2–4.7)
All hematopoietic	54	3.3 (2.5–4.3)	15	1.8 (1.0–3.0)
Lymphoma	44	5.9 (4.3–7.9)	7	1.9 (0.8–3.9)
Hodgkin's	6	4.6 (1.7–10)	1	2.6 (0.1–14)
non-Hodgkin's	38	6.3 (4.2–125)	6	1.9 (0.7–4.0)
Myeloma	4	1.6 (0.4–4.2)	1	0.6 (0.0–3.2)
Leukemia	6	0.9 (0.3–2.0)	7	2.5 (1.0–5.2)

NOTE. First year of follow-up evaluation excluded.

1.2–1.5, Table 2). The relative risk declined with increasing length of follow-up evaluation. After 10 or more years of follow-up evaluation, the SIR was only slightly and nonsignificantly elevated (SIR = 1.1, 95% CI: 0.9–1.4, Figure 1). (Exclusion of also the second year of follow-up evaluation had little impact on the overall or site-specific risks in the subsequent interval [data not shown].) The overall risk for cancer decreased over successive calendar periods of follow-up, but when malignant lymphomas, buccal, esophageal, and small intestinal carcinomas were removed from the total, no tendency toward a decline over calendar period, and indeed no increased risk, was observed (data not shown). Overall, risks remained relatively similar in analyses of subjects diagnosed with CD as the main (vs. contributory) discharge diagnosis on the first hospitalization, of subjects with (vs. without) any other medical condition listed on the initial CD discharge, of subjects discharged with CD from internal medicine departments only (vs. entire cohort), and within each subcohort as defined by the ICD codes. Twelve cases of cancer occurred in individuals first hospitalized with CD before 10 years of age (SIR = 1.0, 95% CI: 0.5–1.8), with no site predilection. Two further cancers were diagnosed in individuals first hospitalized with CD between 10–19 years of age.

With 44 observed cases, malignant lymphomas (of all types) accounted for 18% of all cancers (expected: 4%), and the relative risk was increased 6-fold (SIR = 5.9, 95% CI: 4.3–7.9, Tables 2 and 3). The relative risks were similar for men and for women (Table 3). Individuals with their first hospitalization for CD at younger than 10 years of age had a modest and nonsignificant increase in risk (SIR = 1.4, 95% CI: 0.2–5.0, n = 2, Table 3). In contrast, individuals first hospitalized with CD as adults (older than 20 years) had a considerably higher relative risk (SIR = 7.0, 95% CI: 5.0–9.5, n = 41) that declined with increasing time of follow-up evaluation, reaching unity after 15 or more years (SIR = 1.0, 95% CI: 0.0–5.4, n = 1). The relative risk also decreased over successive calendar periods of lymphoma diagnosis, from SIR = 12 (95% CI: 3.8–28, n = 5) during 1970–1979, through SIR = 8.5 (95% CI: 5.5–13, n = 25) during 1980–1989, to 3.4 (95% CI: 1.9–5.7, n = 14 during 1990–1995, *P* for linear trend 1964–1969 through 1990–1995 = 0.025 adjusted for sex and time of follow-up [no cases were observed during 1964–1969 but only 0.015 cases were expected]). We were able to retrieve the pathology report in 12 of the 14 cases of malignant lymphomas that were registered from 1990 to 1995. Four cases were classified as T-cell non-Hodgkin's

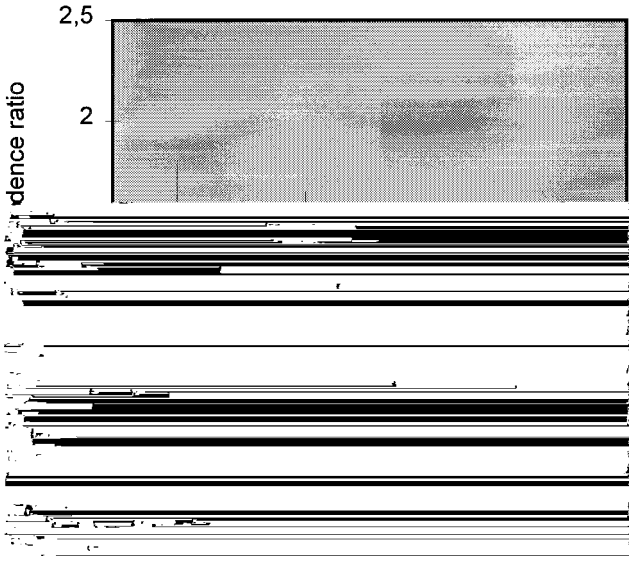

Figure 1. Overall relative risk for cancer by time since first hospitalization for CD in a Swedish cohort of 11,019 individuals hospitalized with CD between 1964 and 1994.

Table 3. SIRs of Malignant Lymphoma and of Selected Gastrointestinal Carcinomas With 95% CI in Subjects With CD (Without a Diagnosis of DH) 1964–1994 Through 1995

	Malignant lymphoma	Oral cavity	Esophagus	Small intestine	Large intestine	Liver (primary)
No. malignancies	44	8	6	8	26	11
Overall relative risk	5.9 (4.3–7.9)	2.3 (1.0–4.5)	4.2 (1.6–9.2)	10 (4.4–20)	1.9 (1.2–2.8)	2.7 (1.3–4.7)
Sex						
Men	6.2 (3.9–9.3)	3.8 (1.7–7.6)	2.2 (0.3–7.8)	14 (4.6–33)	1.9 (1.0–3.5)	3.3 (1.1–7.6)
Women	5.6 (3.5–8.6)	0.0 (0.0–2.6)	8.0 (2.2–21)	7.0 (1.5–21)	1.8 (1.0–3.0)	2.3 (0.8–5.0)
Age at entry (*yr*)						
0–19	1.9 (0.4–5.5)	0.0 (0.0–25)	0.0 (0.0–1844)	0.0 (0.0–1229)	2.9 (0.1–16)	0.0 (0.0–36)
20–59	7.7 (4.9–12)	4.3 (1.7–8.9)	7.0 (1.9–18)	17 (6.2–37)	1.2 (0.5–2.7)	3.9 (1.5–8.6)
>60	6.3 (3.8–9.8)	0.6 (0.0–3.3)	2.4 (0.3–8.6)	4.8 (0.6–18)	2.2 (1.3–3.4)	2.0 (0.6–4.6)
Attained age (*yr*)						
0–59	6.0 (3.7–9.5)	5.0 (1.6–12)	13 (2.8–39)	22 (6.1–57)	1.3 (0.3–3.7)	4.1 (0.8–12)
>60	5.8 (3.7–8.5)	1.2 (0.3–3.5)	2.5 (0.5–7.3)	6.6 (1.8–17)	2.0 (1.3–3.0)	2.3 (1.0–4.6)
Follow-up (*yr*)[a]						
1–4	9.7 (6.3–14)	1.5 (0.2–5.3)	3.6 (0.4–13)	13 (3.6–34)	2.4 (1.3–4.1)	0.6 (0.0–3.2)
>5	3.8 (2.2–6.0)	2.8 (1.0–6.2)	4.7 (1.3–12)	8.3 (2.3–21)	1.5 (0.8–2.6)	4.1 (2.0–7.6)

[a]For malignant lymphomas: SIR = 20 (14–29) for the period 0–<2 years of follow-up, and SIR = 8.9 (5.2–14) for 2–<5 years of follow-up.
NOTE. First year of follow-up evaluation is excluded.

lymphomas (3 enteropathy-associated T-cell lymphomas and one anaplastic ki1 + large-cell lymphoma), 4 as B-cell non-Hodgkin's lymphomas (one located in the small intestine), 2 as non-Hodgkin's lymphomas but of unspecified cell origin, and 2 as Hodgkin's lymphomas. None of the individuals who developed a malignant lymphoma had a discharge diagnosis of immune-globulin deficiency or rheumatoid arthritis during hospitalizations preceding diagnosis of lymphoma.

Several digestive tract carcinomas occurred in excess, including oropharyngeal (SIR = 2.3, 95% CI: 1.0–4.5, n = 8, 7 of which were squamous cell carcinomas), esophageal (SIR = 4.2, 95% CI: 1.6–9.2, n = 6, all squamous cell carcinomas), and small intestinal carcinomas (SIR = 10, 95% CI: 4.4–20, n = 8, 6 of which were adenocarcinomas, one mixed carcinoid-adenocarcinoma, and one unclassified) (Tables 2 and 3). The excess of oropharyngeal carcinomas was restricted to middle-aged men. In contrast, there was a nonsignificant excess of women with esophageal carcinoma ($P = 0.12$ compared with male SIR), although elevated relative risks were observed in all strata. Significantly elevated risks for small intestinal carcinomas were observed both for men and women younger than 60 years at entry and throughout follow-up evaluation.

There was an increased risk for colorectal cancer (SIR = 1.5, 95% CI: 1.0–2.0), which was owing to an increased risk for ascending (SIR = 2.4, 95% CI: 1.2–4.2, n = 11) and transverse (SIR = 2.2, 95% CI: 0.6–5.7, n = 4), but not descending (SIR = 1.3, 95% CI: 0.5–2.8, n = 6) colon or rectal (SIR = 0.8, 95% CI: 0.3–1.6, n = 6) cancer. The increased risk for colon cancer was confined to subjects older than 60 years of age at entry, and to the first 5 years of follow-up evaluation. The risk for primary liver cancer was increased (SIR = 2.7, 95% CI: 1.3–4.7, n = 11, 7 hepatocellular carcinomas, 2 cholangiocarcinomas, and 2 of mixed or other origin), both for men and women, particularly those younger than 60 years at entry, but only beyond the first 5 years of follow-up evaluation. Four of the cases arose in individuals with an inpatient diagnosis of either diabetes, primary biliary cirrhosis, primary sclerosing cholangitis, or alcoholism.

The occurrence of breast cancer was markedly reduced (SIR = 0.3, 95% CI: 0.1–0.5, n = 7), in women of all ages at entry, and both for pre- and postmenopausal breast cancer.

Dermatitis Herpetiformis

One hundred and thirty-five cancers occurred among individuals discharged with DH (SIR = 1.2, 95% CI: 1.0–1.4). The risk was similar for men and women (Table 2), and did not differ substantially according to age at initial hospitalization (data not shown) but was essentially confined to the first 5 years of follow-up evaluation.

There was a 2-fold increased risk for malignant lymphomas (SIR = 1.9, 95% CI: 0.8–3.9, n = 7, 7% of all observed cancers). The excess risk was confined to men older than 60 years of age at entry, and to the first 5 years of follow-up evaluation.

No significantly increased or decreased risk for digestive tract carcinomas, including liver cancer, was observed. There was a borderline significant increased risk

for leukemia (SIR = 2.5, 95% CI: 1.0–5.2, n = 7), which was made up by 3 acute myeloid (SIR = 4.0, 95% CI; 0.8–12), 1 acute lymphocytic (SIR = 10.4, 95% CI: 0.3–58), and 2 chronic lymphocytic (SIR = 1.7, 95% CI: 0.2–6.1) leukemias.

Patients Discharged With Both Celiac Disease and Dermatitis Herpetiformis

Among the 226 subjects diagnosed with both CD and DH who were neither included in the tables nor in the results listed earlier, the overall risk for cancer was not increased (SIR = 1.1, 95% CI: 0.6–1.8, n = 15). There were no malignant lymphomas or leukemia, and no cases of oropharyngeal or esophageal cancer. There was one small intestinal carcinoma (SIR = 16, 95% CI: 0.4–88), and 2 hepatocellular cancers (SIR = 6.6, 95% CI: 0.8–24). The remainder of the cases represented a mix of cancers of various sites, none of which occurred significantly more or less often than expected.

Discussion

In this study, we showed that the overall cancer risk in a population-based cohort of individuals hospitalized with CD or DH over a 30-year period was only modestly elevated. In fact, in the first 5–10 years after initial hospitalization, no significant risk increase could be detected. Likewise, individuals first hospitalized as children or adolescents had no detectable increased cancer risk during their follow-up evaluation. Although we observed markedly elevated relative risks for malignant lymphomas and certain gastrointestinal carcinomas in the entire CD cohort, these relative risks were lower than in many previous studies,[6–13,15,17,18,20,21] but comparable to at least one recent study on lymphomas.[22] Importantly, we observed a tendency toward a declining relative risk for malignant lymphomas over successive calendar periods. Finally, our study highlighted previously unrecognized but markedly elevated (liver cancer) and reduced (breast cancer) risks for specified cancers among individuals with CD.

Most previous studies on the occurrence of cancer have been limited to a few hundred cases of CD or DH[6–10,12–16,19–21]—typically identified at one or a few referral centers or specialty clinics[6–10,12,15–17,19,20]—or have used mortality data for the assessment of cancer.[13,20] The results have therefore lacked precision, often been confined to lymphomas or total cancer only, characterized by a greater chance of misclassification of disease outcome, and had a limited generalizability. Moreover, some of these studies have included cases of cancer diagnosed before the diagnosis of CD,[11,17] or cancers detected in conjunction with CD,[6–9,11–13,15,17,19,20] which may have resulted in biased and inflated risks. Only one study has assessed and compared the risk for cancer after CD or risk subsequent to DH in the same study population (a specialty clinic).[16] Owing to limited statistical power, risk stratified by age (at entry and attained age), and latency have not been presented in most prior studies. Only highly elevated risks have reached statistical significance. The 2 hitherto largest studies (2 mortality analyses from Italy[20] and Scotland[13]) both observed an increased (around tripled) cancer mortality, but when lymphomas were excluded, the remaining relative risks for dying from cancer ranged from unelevated to 90% increased, based on 8 and 23 deaths, respectively. In keeping with this, the strength of our study is the large number of individuals identified in each of the cohorts of patients with CD and with DH, which were population based and identified in the same source population, providing means to compare risks between the cohorts and to stratify the risk according to risk determinants such as age, sex, and time. The follow-up through population-based registers allowed the assessment of cancer incidence rather than cancer mortality, the former being less sensitive to factors affecting stage at diagnosis, and prognosis, although it is susceptible to ascertainment bias, for example, colorectal cancer incidentally diagnosed during the investigation of a CD-related anemia. (In our study, however, with the exception of oropharyngeal cancer, the overall risk estimates for the cancers in Table 4 were in the same order of magnitude whether they were based on cancer incidence or cancer mortality [data not shown].) Also, the ascertainment of cancer was performed independently of the identification of the cohorts, thereby reducing selection bias. To further reduce the potential for selection bias, misclassification, and ascertainment bias, we excluded cancers occurring during the first year after entry into the cohort because they either may have been the underlying reason for the work-up leading to the diagnosis of CD, or have been unexpectedly detected during the work-up for CD. For similar reasons, we also excluded cancers diagnosed incidentally at autopsy from the observed and the expected numbers.

With respect to the inpatient register, the completeness during recent years is estimated to more than 99% of all discharges in the country, and 99% of these recordings include a discharge diagnosis. We are unaware of studies of the validity of the CD or DH diagnoses in this register, but validations of other chronic conditions (inflammatory bowel disease, rheumatoid arthritis, rheumatologic vasculitides, validation studies of unselected subsets of the entire register) have revealed that 85%–

90% of the recorded diagnoses are in fact correct. Because CD is a histopathologic (rather than symptom based) diagnosis, the validity of the diagnosis is likely to be comparable to, or higher than, the earlier-listed conditions. In theory, because we lacked individual information on diagnostic procedures, one explanation for the relatively lower risks may be erroneous inclusion of individuals without CD or DH. However, even the extreme assumption that as much as 25% of the (person-time in the) cohort (excluding, e.g., all lymphoma cases) that were made-up by healthy individuals would result in an SIR of malignant lymphomas around 8, and malignant lymphomas would make up slightly less than a quarter of all cancer cases—figures that are still lower than those of many previous studies.

Because our study was based on hospitalized patients, and hospitalization is nowadays not a sine qua non for the diagnosis to be made but may occur more often in individuals at high risk for cancer for various reasons (severe CD, significant comorbidity, and so forth), less-severe cases treated as outpatients only might not have been included. (In fact, because diagnostic endoscopy often used to be performed on an inpatient basis, at least among children, our cohort is likely to represent a mix of individuals primarily hospitalized for CD- or DH-related diagnostic reasons, therapeutic reasons, and primarily because of other concomitant medical conditions.) An overrepresentation of severe cases in our study might have acted to limit the generalizability of our risk estimates. Most likely, therefore, our comparatively low (and in some subsets unelevated) cancer risks still represent an overestimation of the cancer risk in the entire population with CD or DH.

The 6-fold increased risk for malignant lymphomas among individuals with CD should be viewed against the 15- to 100-fold increase reported in most previous studies.[6,8,9,13] It is, however, of the same magnitude as in a study from Finland[16] and in the study by Holmes et al.[12] of individuals adhering to a strict gluten-free diet, although the number of observed cases in those studies were small (n = 1 and n = 2, respectively). Also, in a recently published case-control study on Italian patients with malignant lymphomas, an odds ratio of CD of 3.1 was observed.[22] Because of their low inclusion rate (47% of all eligible cases) and some uncertainty as to the representativeness of the controls, the results might be interpreted with some caution. The doubled risk for malignant lymphoma among patients with DH is lower than the 5- to 100-fold risk earlier reported.[10,16,17]

Our study also revealed differences in lymphoma risk within and between the cohorts under study. Childhood-onset CD was only associated with a 40% and nonsignificant risk increase. Indeed, in the subset of individuals hospitalized with CD before 10 years of age, the overall risk for cancer was not increased. Although this lower risk may be owing to insufficient follow-up time to detect a substantial risk increase later in life, or a lower prevalence of acquired comorbidity, it also may be caused by a shorter mean interval from onset of disease until its diagnosis and treatment among children (patients with adult-onset disease can often give a history of long-standing unspecific bowel complaints).[28] Finally, in keeping with other studies, we observed high risks for malignant lymphomas shortly after the first hospitalization for (adult) CD (including a high relative risk during the first year of follow-up evaluation [data not shown]).[9,13,20] Although this phenomenon might be owing to the existence of particularly aggressive forms of CD with rapid progression to ulcerative jejunitis in a minority of (adult onset) patients,[29] it also may be caused by an underestimation of the true latency time in these subjects, as well as misdiagnosis of incipient lymphomas as CD.

Interestingly, we observed a decreasing relative risk for malignant lymphomas (and of buccal, esophageal, and small-intestinal carcinomas, but not for all other cancers combined) over calendar time. Although this trend must be interpreted in the light of potential biases (increasing diagnosis of silent or mild CD over time, or temporal shifts in the composition of the cohort with regards to other lymphoma determinants), it may explain some of the discrepancy between our study and those of cohorts of patients with CD diagnosed during earlier calendar periods. Although we have no such exposure data, the declining trend also is compatible with a beneficial effect of increasing awareness and adherence to a gluten-free diet, recently challenged in an American report of 381 patients with CD from a tertiary referral center.[30]

Intestinal lymphomas in the context of CD are commonly regarded to be of T-cell origin.[31] Among the 12 reviewed lymphomas in our cohort, half of the specified cases were of T-cell origin. This result is not only in-line with that recently presented by Catassi et al.,[22] it also indicates—assuming that 5%–10% of all non-Hodgkin's lymphomas in Sweden are of T-cell phenotype—apart from a highly increased risk for T-cell non-Hodgkin's lymphomas in CD, the possibility of an increased risk for B-cell non-Hodgkin's lymphoma.

The increased risks for oropharyngeal, esophageal, and small-intestinal carcinomas observed in the CD cohort confirm earlier reports,[6,8,11–13] and are to be contrasted with the absence of risk increases for these malignancies

in the DH cohort. Rather than a high absolute risk, the higher relative risks among young (compared with adult) individuals may reflect the low background rate of such cancers in the population. The reason(s) for the increased risk, as well as the differences between the cohorts, is unknown. CD might in itself increase the risk for cancers of the upper-gastrointestinal tract (and of the right colon): activated T cells in CD release proinflammatory cytokines not necessarily confined to the small intestine (gliadin provocation in the rectum elicits a local enteropathy-like response[32,33]). Nutritional deficiencies secondary to CD or its dietary treatment also may act to increase the risk, at least of oropharyngeal and esophageal cancers.[34] However, as indicated earlier, the gastrointestinal symptoms in DH are less pronounced than in CD, a fact that together with the different age structures in the 2 cohorts and the notion that a gluten-free diet leads to subsequent reduction of enteropathy and cancer risk,[12,35,36] could explain the lower relative risks for gastrointestinal carcinomas in the DH cohort compared with the CD cohort.

In the CD cohort, but not in the DH cohort, we also observed a marked increase of primary liver cancer, and a borderline increased risk for pancreatic cancer, risks that have not been described earlier. Diseases such as primary biliary cirrhosis, sclerosing cholangitis, and diabetes, which are associated with CD and themselves serve as risk factors for liver cancer, may underlie the observed risk increase.[37,38] Alcoholism is a risk factor for many of the gastrointestinal cancers observed in excess. Yet, alcoholism was a rare discharge diagnosis among individuals in our cohort who developed these cancers. The increased risk for pancreatic cancer could be owing to concomitant diabetes, or to pancreatic insufficiency, which also is associated with CD, although only one of the cases had an inpatient discharge of diabetes (data not shown).[39,40]

The reduced risk for breast cancer was observed in all age groups among individuals with CD, and has not been previously described. Earlier reports, although with very low expected numbers, have noted a deficit of cases.[13] Although this unexpected finding may be owing to chance, decreased risks for breast cancer has been described in some populations with immune suppression or other types of immune dysfunction (e.g., after transplantation, rheumatoid arthritis, and ulcerative pancolitis).[41–43]

In conclusion, this large, nationwide, and population-based cohort study of patients hospitalized with CD and DH indicates that the total cancer occurrence is indeed elevated, but only temporarily so, not after 10 or more years subsequent to initial hospitalization for these conditions, and less so today than in the past. This finding is in accorda5onlyD'TDfiwDfiWfifiqwD8fiWfifiqD8fiW18zjwfiqD

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